## REMARKS/ARGUMENTS

This reply is being submitted together with a Request for Continued Examination.

### I. Status of the Prosecution

Claims 1-85 are pending in the application. Claims 1-81 have been withdrawn as directed to nonelected inventions. Claims 82-85 are presently under consideration. Applicants wish to thank the examiner for acknowledging the claim for priority under 35 U.S.C. §119(e). Applicants respectfully request that the Attorney Docket Number ORT-1296 be changed to JJPR-0013 (ORT 1296) on all future correspondence.

Claims 82-85 are amended herein to place the claims in better condition for allowance and to reduce the issues on appeal. Applicants assert that the amendments are fully supported by the specification and introduce no new matter in accordance with the rules.

This amendment was previously filed with a Notice of Appeal. The Advisory Action in response thereto indicated that the amendment would not be entered for purposes of Appeal.

### II. Notations, Objections and Rejections Have Been Addressed.

Applicants thank the examiner for reiterating the notations, objections and rejections. In an effort to advance the prosecution of the application, Applicants note the following:

With respect to the IDS, Applicants note that they are in the process of obtaining official file records from the United States Patent and Trademark Office to confirm that the IDS was complete as filed, as addressed in the prior communication of November 13, 2002.

With respect to the informal drawings, Applicants acknowledge drawings filed are sufficient for examination and that the requirement for formal drawings has been deferred until allowance.

With respect to Example 4, Applicants invite the Examiner's attention to the communication filed November 13, 2002 wherein on page 2 Example 4 was amended to comply with the requirements.

## III. The Compositions of Mazer *et al.* Do Not Anticipate the Claimed Invention.

Claims 82-85 stand rejected as allegedly anticipated by Mazer *et al.* (US Patent No:5,698,222). Mazer *et al.* teach a calcium supplement, preferably calcium glycerophosphate, for use as a nutritional supplement, for example in beverages and calcium tablets. Mazer *et al.* do not teach or suggest compounds that modulate extracellular ligands. Mazer *et al.* do not teach or suggest pharmaceutical compositions.

The claims are directed to compounds that modulate the response of an extracellular ligand identified by a method comprising the steps of: contacting a compound suspected of being a compound that modulates the response of an extracellular ligand with *a cell* having a nucleus and containing a membrane-bound, constitutively active transcription factor produced by expression of a nucleic acid construct comprising an expression vector containing: a constitutively active domain; a synthetic DNA binding domain that binds to a nucleic acid sequence and activates transcription of an endogenous gene; and a membrane-anchoring domain that contains a protease cleavage site, wherein the constitutively active domain is operably linked to the DNA binding domain such that the transcription factor is active in an unregulated fashion; stimulating activity of a protease by the compound to

release the transcription factor from the membrane, thereby allowing the transcription factor to translocate to the nucleus; and measuring expression of a gene under promotional control of the membrane-bound transcription factor, whereby an increase or decrease in expression of the gene is indicative that the compound modulates the response of an extracellular ligand.

Applicants respectfully note that the although the claim is directed to a product identified by process claim, it is apparent that any allegedly anticipatory compound must still satisfy the requirements of being able to stimulate the activity of the protease, such protease being located intracellularly. Accordingly notwithstanding the fact that calpain is a protease whose activity is strictly Ca++ dependent, this cannot be construed to mean that any source of extracellular calcium, such as the beverages or tablets of Mazer *et al.* can activate the intracellular protease of the instant claims. It is well-known in the art the release of intracellular calcium, or for that matter, intracellular calcium concentrations are not simply a function of extracellular calcium. Even with respect to calcium influx (i.e. uptake) into *intestinal* cells, Mazer *et al.* teach that other compounds and factors have large influences on the uptake – for example, Vitamin D, fiber, phytate, simple sugars, organic acids, and proteins, particularly sulfur-amino acid containing proteins have an effect on calcium bioavailability. There is no teaching or suggestion in Mazer *et al.* regarding any intracellular properties of the calcium compositions taught therein. The examiner is invited to provide a reference for the record supporting the notion that extracellular calcium supplements increase intracellular calcium concentrations in a manner that necessarily stimulates the activity of an intracellular protease.

The compounds of the instant claims must be *necessarily* able to stimulate the activity of an intracellular protease when brought into contact with the cellular membrane (i.e. extracellularly). There is no objective reason to believe that the calcium compositions of Mazer *et al.*, or any other calcium compositions known in the art are *necessarily* able to do this (i.e. are inherently able to stimulate intracellular protease), and Mazer *et al.* lack any express teaching of such properties. Even assuming for argument that the calcium compounds of Mazer *et al.* can be transported into the cell, there is no objective evidence teaching or suggesting that these would increase the intracellular concentration in a way that would stimulate the activity of the protease. Rather, the skilled artisan would expect that any such calcium would be *sequestered* in the cell so as to avoid wreaking havoc on the cell's ability to maintain a homeostasis, the concentration of free calcium and other ions being critical to maintenance of proper homeostasis.

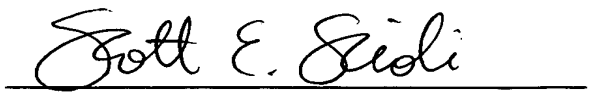
Further to this argument is the definition of compound as provided in the specification on page 7 – a compound has the potential to "modulate the *specific response* of an extracellular ligand." Again there is no objective reason to believe that an external supplement of calcium, such as that of Mazer *et al.* would be able to modulate the specific response of an extracellular ligand.

Because the compositions taught by Mazer *et al.* cannot be said to inherently stimulate the activity of an intracellular protease, Applicants respectfully request that the rejection under 35 U.S.C. § 102 be reconsidered and withdrawn.

## IV. Conclusion

Applicants believe the amendments and arguments presented herein are fully responsive to the Office Action and that all outstanding issues have been addressed with respect to the claims. Applicants respectfully submit that all of the claims are in condition for allowance and early and favorable action in that regard is earnestly solicited. The Examiner is invited to contact the Applicants undersigned representative to resolve any matters leading to the proper issuance of Applicants claims.

Date: September 10, 2003



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